Review Article

Acute bacterial conjunctivitis

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ABSTRACT.

Acute bacterial conjunctivitis is the eye disease most commonly seen by general practitioners, and is estimated to represent approximately 1% of all consultations in primary care. This article gives a review of the epidemiology, aetiology, clinical picture, complications, differential diagnoses, in vitro examinations and therapy of acute bacterial conjunctivitis. Until now, topical antibacterial therapy has generally been preferred by both physicians and patients because this will usually shorten the course of the disease slightly and allow the early readmittance of children to their kindergarten or school. Recently, several reports from primary care have confirmed the well-known clinical experience that the disorder has an excellent prognosis with a high frequency of spontaneous remission. In accordance, an expectant attitude or delayed prescription policy are now frequently strongly recommended. However, these reports also emphasize the difficulty in making a correct clinical distinction between bacterial and viral conjunctivitis. The effect of a general non-prescription attitude on transmission rates of pathogens also remains to be clarified. This must be born in mind when deciding how these patients should be handled. The socioeconomic and medical pros and cons of different treatment policies are discussed, and a highly personal view on the optimal handling strategy for these patients is also presented.

Key words: acute bacterial conjunctivitis – aetiology – clinical picture – complications – differential diagnoses – epidemiology – in vitro examinations – treatment

In chronic bacterial conjunctivitis, ocular symptoms and signs last for at least 4 weeks and relapses occur frequently. Conjunctival hyperaemia and discharge are usually moderate or mild. Coagulase-positive and -negative staphylococci are the organisms found most frequently. Exotoxins produced by staphylococci may cause punctate epithelial keratitis and marginal keratitis. Moraxella lacunata is the species most commonly found in chronic angular blepharoconjunctivitis (Rubenstein 1999). Although such chronic conjunctival bacterial infection does occur, other causes of the ocular complaints – such as blepharitis, meibomitis, acne rosacea, ocular allergy, dacryocystitis, ectropium, entropium, trichiasis and dry-eye disease – should always be excluded.

Worldwide, acute bacterial conjunctivitis represents the vast majority of all cases of bacterial conjunctivitis, and the rest of this article deals exclusively with this form of bacterial conjunctivitis.

Epidemiology

Acute conjunctivitis is commonly defined as conjunctivitis with symptoms of less than 3–4 weeks duration, and is the eye disorder most commonly seen by a general practitioner (GP) (Dart 1986; McDonnell 1988). According to the diagnoses made by the GPs, the majority of cases are caused by infections, followed by allergic conditions. Some seasonal variations have been described; bacterial conjunctivitis shows a peak occurrence during December–April and

Introduction

Bacterial conjunctivitis is usually divided according to its course and severity into hyperacute, acute and chronic forms. Neisseria gonorrhoeae is the most frequent cause of hyperacute bacterial conjunctivitis, which is then usually regarded as an oculogenital disease, occurring in neonates and in sexually active adults. Hyperacute bacterial conjunctivitis is characterized by abrupt onset, profuse, thick, yellow-green purulent secretion, mixed ocular injection and chemosis and sometimes the formation of an inflammatory membrane (Rubenstein 1999; Mannis & Plotnik 2005). If caused by N. gonorrhoeae, painful corneal involvement rapidly develops, and corneal opacities and even corneal perforation and endophthalmitis may occur if the infection is not rapidly recognized and treated.
Acute infective conjunctivitis represents up to 1% of GP consultations in the UK. Each year, one in 10 000 in 1981–1982 to 395 per 10 000 in 1991–1992 (McCormick et al. 1995). Acute infective conjunctivitis is seen more frequently during the spring and summer months (Gigliotti et al. 1981; Schmitz et al. 1983; Fitch et al. 1989; Block et al. 2000; Aoki & Tagawa 2002). Worldwide, there are an estimated 5 million cases of neonatal infectious conjunctivitis per year (Wihelmus 2005). In the developed world, acute red eyes account for 1–4% of all GP consultations, and are most frequently diagnosed as acute bacteraial conjunctivitis (Dart 1986; McDonnell 1988; Sheikh & Hurwitz 2001; Everitt & Little 2002; Rietveld et al. 2005). In Norway, it has been suggested that acute infective conjunctivitis is suspected in approximately 30 out of 1000 patients in a general medical practice, and that this diagnosis appears to be correct in approximately two out of three of these cases (Hovd- ing et al. 1991). In the UK, the proportion of patients who consulted for conjunctivitis increased from 284 per 10 000 in 1981–1982 to 395 per 10 000 in 1991–1992 (McCormick et al. 1995).

Acute infective conjunctivitis is seen most frequently in infants, school children and the elderly. It is usually the result of bacterial or viral infections, the latter most often caused by adenoviruses, Herpes simplex virus or picornaviruses (Rubenstein 1999). Several reports indicate that bacteria are responsible for about 50–75% of all cases of acute conjunctivitis in young children (Gigliotti et al. 1981; Block et al. 2000; Buznach et al. 2005). In accordance with this, a study by Rose et al. (2005) including 326 children with a clinical diagnosis of conjunctivitis yielded bacterial pathogens in 67% of the patients, viruses alone in 3% and both bacteria and viruses in 10%. On the other hand, an adenovirus was isolated from 11 of 17 paediatric patients (65%) who simultaneously had acute conjunctivitis and pharyngitis (Gigliotti et al. 1981). Furthermore, in 16 of 45 patients (36%) presenting to an ocular emergency room with symptoms and signs of acute conjunctivitis a viral aetiology was found (adenovirus in 15 patients and H. simplex virus type I in one patient), while a bacterial aetiology was diagnosed in 18 cases (40%) and no cases of chlamydial conjunctivitis were found (Fitch et al. 1989). The difficulty in making a correct clinical distinction between bacterial and viral conjunctivitis is illustrated by an article based on a questionnaire sent to 300 GPs in the UK (Everitt & Lit- tle 2002). The answers from the 236 responders (78%) showed that 92% felt confident or very confident of making the diagnosis of acute infective conjunctivitis, but only 36% felt able to discriminate between acute bacterial and viral conjunctivitis. As much as 95% of the responders usually prescribed topical antibiotics to patients with suspected acute infective conjunctivitis and 87% used chloramphenicol as their drug of choice, while 13% primarily used fusidic acid. Features believed to increase the probability of a bacterial infection were a history of a cold (85%) and the type of discharge (87%). Although obviously rare compared to bacterial and viral infections, chlamydial conjunctivitis is still an important differential diagnosis, particularly in newborns (Solberg et al. 1991; Dannevig et al. 1992; Ruben 1999). In some communities, Chlamydia trachomatis has been isolated from 46–73% of neonates with purulent conjunctivitis, probably reflecting a high prevalence of chlamydial cervicitis in the local population (Rapoza et al. 1986).

Based on a Medline literature search, Richardson et al. (2001) reported only a low or moderate risk of transmission in infectious conjunctivitis, and they found no general recommendation for exclusion from preschool or school. However, the conclusions drawn were poorly evidence-based; infectivity and need for exclusion, etc. will obviously be different in adenoviral and bacteriological infections. In epidemic keratoconjunctivitis caused by adenovirus type 8 and type 19, the risk of infecting close social contacts has been reported to be 10–35% (McMinn et al. 1991; Wihelmus 2005). There are also numerous reports on outbreaks of acute bacterial conjunctivitis in day-care centres, boarding schools, military camps, nursing homes, intensive care units, etc., but exact and evidence-based knowledge about the infectivity and community spread of acute bacterial conjunctivitis is generally lacking. A study including 20 children with acute conjunctivitis from five different day-care centres yielded Haemophilus influenzae from eight eyes and Moraxella from two eyes (Trottier et al. 1991). Different H. influenzae strains occurred within the same centre, but the same strain of H. influenzae was always found in both the eye and nasopharynx. Thus, the eyes were probably infected from the nasopharynx. On the other hand, the authors suggest that a viral infection spreading from child to child may impair the resistance of the eye to bacterial colonization and thus permit bacterial superinfection. Reporting from seven nursing homes, Garibaldi et al. (1981) noted high prevalence and clustering of infections such as upper respiratory tract infections, diarrhoea, conjunctivitis and infected decubital ulcers. High patient-to-staff ratios, high employee turnover, non-professional personnel and increased susceptibility of patients were identified as risk factors for the spreading of infections. Patients in nursing homes for the elderly and long-term-care facilities have been reported to be highly susceptible to conjunctivitis caused by Streptococcus pyogenes (Ruben et al. 1984) and to methicillin-resistant Staphylococcus aureus (Brennen & Muder 1990). According to King et al. (1988), conjunctivitis accounted for 5% of nosocomial infections in a large university-affiliated paediatric hospital between January 1984 and April 1986. Pseudomonas aeruginosa was recovered from the conjunctiva of 30 patients with chronic and debilitating primary disease. Compared to the total number of patients admitted to the hospital, children under the age of 18 months were significantly over-represented. Seventy per cent of the cases occurred in the intensive care unit patients, and P. aeruginosa was recovered from 70% of patients who had antecedent nasopharyngeal/endotracheal cultures obtained. All patients
had received antibiotic treatment during hospitalization, and a need for respiratory care characterized the population. A cluster of 10 severe cases of nosocomial bacterial keratitis in three intensive care units showed almost identical bacterial growth in cultures from eye and sputum (Hilton et al. 1983). All the patients had required frequent tracheal suctioning. Only the left eye was involved in nine of the 10 cases; the ocular infections were ascribed to right-handed nurses’ habit of withdrawing the catheter diagonally across the patient’s face.

Studies on epidemic follicular conjunctivitis occurring in female teenagers have shown a significantly increased incidence of conjunctival cultures yielding *Moraxella lacunata* (Ringvold et al. 1985; Schwartz et al. 1989), implicating the use and sharing of mascara as a possible cause of the infective conjunctivitis. During the first 6 months of 1980, large outbreaks of conjunctivitis were reported from seven colleges and universities in New York State; conjunctival swabs yielded non-typable *Streptococcus pneumoniae* alone or in combination with other organisms in 46% of the cases (Shayegani et al. 1982). Very similar streptococcus strains were isolated during outbreaks of conjunctivitis in other US states.

Despite the lack of strictly evidence-based knowledge, conjunctival infection by direct contact is generally believed to be particularly common in kindergartens and among school children and institutionalized patients. In bacterial conjunctivitis, the suggested periods of incubation and communicability are 1–7 days and 2–7 days, respectively, while the corresponding figures for adenovirus conjunctivitis are 5–12 days and 10–14 days (Wilhelmus 2005).

**Aetiology**

Bacteria may frequently be isolated from the conjunctiva of healthy subjects. Generally speaking, the normal conjunctival flora represents both bacterial colonization and transient or recurring bacterial contamination. Colonization implies a stable presence of the micro-organism, balanced by the host defence mechanisms, while contamination represents micro-organisms introduced from sources outside the conjunctiva (Kowalski & Roat 2005). The majority of micro-organisms present on the healthy conjunctiva represent a continuous or recurring contamination, while true colonization is much more common on the eyelid margins. Given the right conditions, any micro-organism can cause an infection. The ocular pathogenicity of a micro-organism can be calculated by the number of manifest ocular infections divided by the number of eyes harbouring the same micro-organism (Wilhelmus 2005). A primary pathogen will regularly cause infection, an opportunistic pathogen causes infection in immunocompromized individuals, while normally occurring micro-organisms may act as incidental pathogens, replicating and causing disease when host defence mechanisms have been impaired (Wilhelmus 2005).

Coagulase-negative staphylococci and corynebacteria are frequently present on the healthy conjunctiva, but more traditionally pathogenic organisms, such as coagulase-positive staphylococci, streptococci, haemophilus species, moraxellae and gram-negative coliform rods, are also occasionally isolated from normal, non-inflamed eyes (Locatcher-Khorazo & Seegal 1972; Fahmy et al. 1975; Cagle & Abshire 1981; Høvding 1981; Seibel & Ruprecht 1983; Olfersen et al. 1986; Weiss et al. 1993; Thié & Schumacher 1994; Mannis & Plotnik 2005). A greater number of bacterial species is generally recovered from adults than from children. Facultative anaerobic species, particularly corynebacteria, are found significantly more frequently in adults, while streptococci are obtained more frequently from children (Singer et al. 1988). A similar but more stable and abundant bacterial flora can usually be isolated from the eyelid margins of healthy subjects (Cagle & Abshire 1981). In such non-inflamed eyes, an increased frequency of coagulase-negative staphylococci has been found on the conjunctiva of patients with diabetes mellitus compared to a non-diabetic control group (Martins et al. 2004), while a significantly increased occurrence of *S. aureus* has been reported in patients with atopic dermatitis (Inoue 2002). Miller & Ellis (1977) found that the frequency of positive conjunctival bacterial cultures and the amount of lysozyme present in the tear fluid were not influenced by the use of immunosuppressive drugs, but there was a positive correlation between the number of different bacterial species and an increasing dose of prednisolone. Franklin et al. (1977) and Friedlaender et al. (1980) reported that immunodeficient patients had a higher incidence of conjunctival and lid infections, while the microbiological flora was similar to that found in immunocompetent patients. In accordance with these reports, Gritz et al. (1997) and Yamauchi et al. (2005) found a similar bacterial flora in AIDS patients, HIV-positive and HIV-negative patients.

The amount of bacteria present on the healthy conjunctiva is usually rather small, commonly yielding less than 10 colonies on culture, while cases of acute bacterial conjunctivitis often yield a more confluent growth (Kowalski & Roat 2005). In addition to the sweeping and flushing action of eyelids and tear fluid and the barrier function of the conjunctival and corneal epithelium, lysozyme, lactoferrin, beta-lysin, IgA and other immunoglobulins and complement system components in the lacrimal fluid help to prevent the normal bacterial flora from causing conjunctivitis or keratitis (McClellan 1997; Kowalski & Roat 2005; Mannis & Plotnik 2005). In addition, metabolic products made by the normal conjunctival bacterial flora probably also inhibit colonization and multiplication of more virulent bacterial species (McClellan 1997). Mucosa-associated lymphoid tissue (MALT) is an important part of our general defence against pathogens. Eye-associated lymphoid tissue (EALT) appears to be a component of this common mucosal immune system, but the exact mechanisms by which ocular mucosal immunity acts to prevent eye infection are not fully understood (McClellan 1997; Jett 2005).

Acute bacterial conjunctivitis is most frequently caused by *S. aureus*, *Staphylococcus epidermidis*, *H. influenzae*, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Moraxella catarrhalis* and *Gram-negative intestinal bacteria* (Seibel & Ruprecht 1983; Horven 1993; Weiss et al. 1993; Block et al. 2000; Wald et al. 2001; Normann et al. 2002; Buznach et al. 2005; Rose et al.
children, *H. influenzae* is the most commonly isolated bacteria in acute conjunctivitis, followed by *S. pneumoniae* and *M. catarrhales*. In this age group, *H. influenzae* conjunctivitis may often occur alongside recurring otitis media and respiratory infections (Block et al. 2000; Wald et al. 2001; Buznach et al. 2005; Rose et al. 2005). Conjunctivitis caused by *S. aureus* is most frequently seen in neonates and in older children, as well as in adults and the elderly (Dannevig et al. 1992; Normann et al. 2002; Orden Martinez et al. 2004; Mannis & Plotnik 2005; Rietveld et al. 2005). Worldwide, *S. aureus* is the most frequently occurring cause of bacterial conjunctivitis (Mannis & Plotnik 2005).

Even in patients with so-called typical clinical signs and symptoms of acute bacterial conjunctivitis, most studies show a surprisingly high frequency (22–68%) of negative bacteriological cultures (Mahajan 1983; Olafsen et al. 1986; Høvding 1993; Block et al. 2000; Rietveld et al. 2004; Buznach et al. 2005; Kernt et al. 2005; Rose et al. 2005). The varying frequency of ‘positive’ bacteriology in different studies may at least partly be explained by different interpretations of the culture results; some authors report only the frequency of traditionally pathogenic bacteria, while others include all bacteria isolated and a few make a quantitative interpretation of the bacteriological findings. Care should also be taken to avoid contact with the eyelid margins during conjunctival swabbing, because the eyelids commonly harbour staphylococci, corynebacteria and alpha-haemolytic streptococci (Weiss et al. 1993).

Contact with contaminated fingers is believed to be a common cause of acute infective conjunctivitis, but bacteria may also reach the conjunctiva from the eyelid margins and adjacent skin, from the nasopharynx via the nasolacrimal duct, from infected eye drops or contact lenses, and more rarely from the genitals or via the bloodstream. Factors predisposing for infection include ectropion and entropion, an obstructed nasolacrimal duct, abnormal lacrimal fluid and injured conjunctival epithelium following trauma, dry-eye disease or previous infection (Høvding 2004; Mannis & Plotnik 2005). Immunodeficiency syndromes and systemic immunosuppression also predispose for acute bacterial conjunctivitis (Franklin et al. 1977; Friedlaender et al. 1980; Sharma et al. 2004). In vaginally delivered newborns, the primary source of infective organisms is usually believed to be the birth canal of the mother (Isenberg et al. 1988; Normann 2005), but this has been contradicted by Krohn et al. (1993), who suggested that bacteria causing acute conjunctivitis more commonly originate from the infants’ nasopharynx or from the infants’ care providers.

### Clinical picture

According to most textbooks, acute bacterial conjunctivitis begins unilaterally with a ‘foreign body’ sensation, increased secretion and moderate conjunctival hyperaemia (Rubenstein 1999; Mannis & Plotnik 2005). The secretion soon becomes mucopurulent or purulent. ‘Sticky’ eyelids in the morning is recognized as a very common symptom, even in cases without a distinctly abnormal secretion. Distinct or severe pain is rare, although some patients experience a strong burning or stinging sensation. Within 1–2 days the fellow eye usually becomes involved. Although clinicians generally agree that these symptoms and signs may be regarded as typical for acute bacterial conjunctivitis, an extensive literature search conducted by Rietveld et al. (2003) failed to prove that they can be classified as evidence-based diagnostic criteria for the distinction between bacterial and viral conjunctivitis.

Conjunctival injection is the rule, i.e. the redness is most intense on the inside of the eyelids and peripherally on the bulbar conjunctiva, while the eye is paler towards the corneoscleral limbal area (Fig. 1). In more severe cases, the eye shows a mixed injection, i.e. the whole conjunctiva is red, and small haemorrhages and chemosis may also occur. Purulent discharge in the palpebral opening (Fig. 2), or perhaps only in the inferior fornix or as yellow incrustations on the eyelid margins, indicating an infective conjunctivitis. In chronic conjunctivitis – particularly if caused by *S. aureus* – punctate keratitis, blepharitis and marginal keratitis are often seen.

Two studies conducted in general practice on patients with suspected acute bacterial conjunctivitis (Carr 1998; Wall et al. 1998) showed that a purulent secretion was present in 85–90% of patients, sticky eyelids (Fig. 4) in approximately 90% and a foreign body sensation and itching in approximately 90%. More than 50% of the patients reported varying degrees of burning or stinging.

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**Fig. 1.** Acute infective conjunctivitis with characteristic conjunctival injection and a small amount of thick, yellow discharge in the inferior fornix.

**Fig. 2.** Acute bacterial conjunctivitis with mixed injection and copious mucopurulent discharge.

**Fig. 3.** Dry, yellow incrustations on the eyelid margins, indicating an infective conjunctivitis.
Conjunctival or mixed injection was noted in almost all patients, while about 85% showed some erythema of the eyelid skin. On the other hand, a recent study including adult patients presenting at 25 Dutch health centres with a red eye and either (muco)purulent discharge or glued eyelids concluded that only early morning glued eye(s) significantly increased the probability of a bacterial cause of the symptoms, while itching and an earlier history of conjunctivitis decreased it (Rietveld et al. 2004). Therefore, neither the type of injection nor the appearance of the secretion was significantly associated with a positive bacteriology obtained by conjunctival swabblings. In a study reported by Fitch et al. (1989), patient symptoms at presentation to an ocular emergency room were very similar in acute bacterial and viral conjunctivitis, although foreign body sensation was recorded significantly more often in those with a viral infection.

In younger children, particularly in kindergartens, acute conjunctivitis may occur in minor epidemics, and is then commonly caused by *H. influenzae* or *S. pneumoniae*. As previously mentioned, *H. influenzae* conjunctivitis is often associated with systemic infections, particularly acute otitis media and infections of the upper respiratory tract. In a study by Buznach et al. (2005), the so-called conjunctivitis-otitis syndrome was present in 32% of patients; in 82% of these cases the conjunctival culture yielded *H. influenzae*. Corresponding frequencies reported by Block et al. (2000) were 39% and 59%, respectively.

**Complications**

Acute bacterial conjunctivitis is almost invariably a disease with a highly favourable prognosis. Spontaneous cure is likely to occur within 1–2 weeks in at least 60% of cases (Sheikh & Hurwitz 2001; Rose et al. 2005), and serious complications are very seldomly seen (Schiebel 2003; Sheikh & Hurwitz 2006). However, large amounts of bacteria on the conjunctiva will imply a certain risk of keratitis, particularly in conditions predisposing for corneal epithelial defects. Accordingly, eyes with corneal epithelial disease and patients with dry eyes will be at greater risk of developing keratitis. An important precaution in the prevention of keratitis in patients with acute bacterial conjunctivitis is also to discontinue the use of contact lenses and to omit contact tonometry on such eyes (Hovding & Bertelsen 2004).

**Differential diagnoses**

In patients with an acute red eye, the possibility of keratitis or iridocyclitis must always be considered. Earlier episodes of acute unioocular redness in the same eye should particularly raise the suspicion of a recurrent *H. simplex* keratitis or a recurring acute iridocyclitis. Previously known Mb. Bechterew also increases the probability of iridocyclitis. Simple techniques, such as fluorescein staining and assessment of pupillary size and reactions, will in the absence of a slit lamp greatly help GPs to diagnose these important diseases (Buckley 1990).

Viral conjunctivitis is undoubtedly very common, but its exact incidence is difficult to assess because the symptoms are usually mild and spontaneous remission frequently occurs before the patients seek medical attention. In addition, many cases of viral conjunctivitis are misdiagnosed and mistreated as bacterial conjunctivitis. As in acute bacterial conjunctivitis, the viral conjunctivitis usually begins acutely in one eye, while the second eye is commonly involved within the next week. The conjunctival hyperemia is typically accompanied by an increased watery secretion and enlarged preauricular lymph nodes.

Viral conjunctivitis is frequently caused by adenoviruses. In Japan, 1 million cases of adenoviral conjunctivitis have been estimated to occur each year (Aoki & Tagawa 2002). While most cases of adenovirus conjunctivitis only give mild, uncharacteristic and transient symptoms, two well-defined forms are described: pharyngoconjunctival fever (adenovirus type 3, 4 and 7) and epidemic keratoconjunctivitis (adenovirus type 8, 19 and 37) (Rubenstein 1999; Aoki & Tagawa 2002). Both forms are transmitted via respiratory droplets or direct finger-eye contact. Multiple outbreaks of adenovirus conjunctivitis are most frequently caused by adenovirus type 8 or 19, and new cases of the disease commonly originate from consulting rooms or health institutions, where both the use of contaminated tonometers and insufficient hand hygiene are important factors in the spreading of the disease. Initially, the conjunctivitis is commonly accompanied by a mild punctate epithelial keratitis. These tiny epithelial infiltrates are not visible without a slit lamp. Subepithelial infiltrates, which presumably are of immunological origin, may appear in the second week of the disease (Dawson et al. 1972; Starr 2004). These infiltrates are not stained by fluorescein. Dense or confluent central corneal infiltrates may markedly reduce visual acuity. Tear fluid is usually watery, but mucopurulent or even distinctly purulent secretion may also occur (Figs 5 and 6). Stinging and discomfort may be very pronounced, and an initial preauricular glandular enlargement is commonly found. In general practice (i.e. without the use of a slit lamp), epidemic keratoconjunctivitis should be suspected on the basis of a careful case history, supported by the lack of improvement on topical antibacterial treatment. The diagnosis is easily confirmed by conjunctival scrapings for viral culture, polymerase chain reaction (PCR) or adenovirus antigen.

**Fig. 4.** ‘Sticky eyelids’ in acute bacterial conjunctivitis.

**Fig. 5.** Massive chemosis and thick, whitish discharge in adenoviral epidemic keratoconjunctivitis.
Chlamydial conjunctivitis is primarily suspected in patients with typical symptoms and signs of acute bacterial conjunctivitis not satisfactorily responding to standard antibacterial treatment. The condition should particularly be considered in newborns with prolonged conjunctivitis (Dannevig et al. 1992; Rubenstein 1999). In a study on neonatal conjunctivitis, signs of chlamydial conjunctivitis usually presented about 1 week postpartum, while signs of bacterial conjunctivitis appeared about 1 week later (Rapoza et al. 1986). PCR examination of conjunctival scrapings is diagnostic. In cases of neonatal chlamydial conjunctivitis, both the child and its parents must be treated simultaneously.

Allergic conjunctivitis is usually associated with intense itching and watery tear secretion. Chemosis is frequently present. In contact allergy, often caused by eye drops, the skin around and especially below the eye becomes erythematous or eczematous and itching. An exact record of the case history is obviously of great importance in patients with suspected allergic conjunctivitis.

A certain conjunctival follicular or papillary hypertrophy is often seen in viral, chlamydial and allergic conjunctivitis, while this is not a frequent finding in acute bacterial conjunctivitis.

In a contact lens wearer, the development of an acute red eye should primarily be suspected to be caused by the lens wear, and the use of lenses must be temporarily discontinued (Hovding & Bertelsen 2004). A stringently unilateral injection and purulent discharge in a child should raise the suspicion of a retained foreign body in the superior conjunctival fornix.

Because marked improvement or clinical cure of acute bacterial conjunctivitis usually occurs during the first few days of treatment, commonly even without treatment, the course of the symptoms and signs as well as the response to treatment give important diagnostic clues. Patients with suspected acute bacterial conjunctivitis should therefore always be told to return for follow-up examinations if significant improvement does not occur within the next 1–2 days.

In vitro examinations

Routine bacteriological examinations are usually not indicated in the management of clinically suspected acute bacterial conjunctivitis. According to O’Brien & Hahn (2005), microbiological evaluation should be considered for neonates and immunocompromised patients, as well as in all patients with severe acute conjunctivitis. If treatment fails, a conjunctival swab should be taken for bacteriological culture – preferably a few days after the previously prescribed topical medication has been stopped (Mannis & Plotnik 2005). In addition, conjunctival scrapings should be taken for adenovirus, H. simplex virus and chlamydia cultures, PCR and/or antigen analyses. A general clue to the cause of a red eye may also be obtained by Giemsa-stained conjunctival scrapings, where neutrophils suggest a bacterial infection, while lymphocytes and eosinophils indicate viral and allergic conjunctivitis, respectively (Weiss et al. 1993; Cvenkel & Globocnik 1997).

A study by Block et al. (2000) on paediatric acute conjunctivitis showed that ciprofloxacin, ofloxacin and tetracycline had the greatest in vitro activity, followed by gentamycine, tobramycine, polymyxin B–trimethoprim and polymyxin B–neomycine. Papa et al. (2002) found netilmicin to have a significantly better in vitro effect than gentamycin, giving a broad-spectrum in vitro coverage comparable to that of ciprofloxacin, ofloxac in and norfloxacin. Orden Martinez et al. (2004) reported that ciprofloxacin, chloramphenicol and rifampin were active against the commonly occurring bacteria.

However, it should be stressed that there is only limited value of in vitro susceptibility testing of the bacteria isolated in external ocular disorders such as acute bacterial conjunctivitis, because in vitro susceptibility is based on minimum inhibitory concentration (MIC) values for serum concentrations, while breakpoints for in vitro susceptibility of topical medications have not been determined (Block et al. 2000). Thus, all currently available susceptibility tests use much lower concentrations of antibiotics than that obtained in the conjunctiva and cornea by using the same antibiotic agents as eye drops. Therefore, clinical and microbiological cure is often obtained despite an in vitro susceptibility test indicating bacterial resistance to the drug tested.

Treatment

General aspects

Keratitis and other potential complications of acute bacterial conjunctivitis are seen very seldomly in otherwise healthy subjects. Extensive clinical experience has thus proven acute bacterial conjunctivitis to be a disease with a highly favourable prognosis and a high frequency of spontaneous cure.

A meta-analysis published by Sheikh & Hurwitz (2001), based on the few placebo-controlled, randomized, double-blind studies available at that time, showed clinical remission within 5 days in 64% of placebo-treated patients. However, the same analysis also showed that topical antibiotic treatment resulted in a significantly improved early clinical remission, as well as improved early and late microbiological remission. Because this meta-analysis only included patients recruited from specialist care populations, the results are not necessarily representative for primary care patients with suspected acute bacterial conjunctivitis. Therefore, a well-designed and well-controlled study on acute infective conjunctivitis in children aged 6 months to 12 years recruited from 12 general medical practices in the UK was recently carried out (Rose et al. 2005). At baseline, conjunctival swabs yielded one or more of the study-designed pathogenic bacteria (H. influenzae, S. pneumoniae and M. catarrhalis) in 78% of the patients, while adenovirus or picornavirus was
recovered alone or together with the above-mentioned bacteria in 13% of the cases. Clinical cure was recorded in 83% of the placebo group within 7 days, compared with 86% of those receiving chloramphenicol eye drops. The so-called number needed to treat (NNT) to achieve one more clinical cure than that occurring spontaneously was calculated to be 25. Corresponding frequencies of clinical cure on day 7 in patients growing one or more of the study-designed pathogenic bacteria (H. influenzae, S. pneumoniae and M. catarrhalis) were 80% and 85%, respectively (NNT = 22). When the proportion of children achieving clinical cure each day in the chloramphenicol and placebo groups were compared, a significantly better response was obtained in the chloramphenicol group at day 2 (26.4% versus 15.9%); this difference remained statistically significant up to day 7, although the mean difference in the time to cure in the two groups was only 0.3 days during this period. Bacterial eradication at day 7 was also obtained significantly more frequently in the chloramphenicol group (40.0%) than in the placebo group (23.2%), resulting in NNT = 6. The frequency of new conjunctivitis episodes during the following 6 weeks was almost identical in the two study groups. A weakness of this important study is a possible selection bias: only one third of the children presenting to the participating GPs with acute infective conjunctivitis during the trial period were included in the study. Thus, family doctors may conceivably have recruited the less severe cases for the study, believing that patients with more severe symptoms needed topical antibiotics. In addition, patient recruitment only took place during office hours, while one may speculate if patients presenting out of office hours generally will have more severe symptoms and a more abundant conjunctival flora of pathogens.

Another double-blind, randomized and placebo-controlled study on infectious conjunctivitis in primary care was published by Rietveld et al. (2005). Adult patients presenting at 25 Dutch GP centres with a red eye and either (muco)purulent discharge or ‘sticky eyelids’ were invited to participate. At baseline, only 50 of the 163 patients (30.7%) completing the trial were culture-positive. Based on both the clinical examination by the GPs after 7 days and the daily diary kept by each of the patients, the efficacy of fusidic acid gel compared to placebo gel was evaluated. At this stage, clinical cure was recorded in 62% of the fusidic acid group and 59% of the placebo group. Neither the severity nor the duration of symptoms differed significantly in the two patient groups. However, the treatment effect appeared stronger in culture-positive patients, where bacterial eradication in the fusidic acid and in the placebo group was obtained in 76% and 41%, respectively, although more than 60% of the cultures obtained at baseline showed in vitro resistance to fusidic acid. Minor adverse events, mainly a burning sensation after instillation of the study medication, occurred in 14% of the fusidic acid group and in 3% of the placebo group. The main weaknesses of the study were the limited number of culture-proven cases at baseline and the fact that patient recruitment was performed during office hours only. The authors concluded that although the study lacked the power to conclusively demonstrate equivalence between fusidic acid and placebo, it did not support the current GP prescription practice of using topical antibiotics in the vast majority of patients with suspected infective conjunctivitis.

In another interesting, open, randomized and controlled study from 30 general practices including 307 children and adults with acute, presumably infective conjunctivitis, the results obtained by no treatment, delayed topical antibiotic treatment or immediate topical chloramphenicol treatment were compared (Everitt et al. 2006). The different treatments did not influence the severity of symptoms during the first 3 days, but the duration of moderate symptoms was shortest in the immediate treatment group (3.3 days) and longest in the no treatment group (4.9 days). In the delayed antibiotic treatment group, 53% eventually received topical antibiotics. When asked about their belief in the effectiveness of antibiotics for acute conjunctivitis, as well as their intention to reattend for eye infections, those receiving immediate topical antibiotic therapy had the highest positive score. In accordance with this, the reattendance rate within 2 weeks was lower in the delayed treatment group than in those receiving immediate treatment. The distribution of an information leaflet about acute conjunctivitis did not significantly influence the attitude of the patients regarding acute conjunctivitis. The authors judged a delayed prescription attitude to be the most favourable alternative in many respects, reducing both the use of topical antibiotics and the frequency of early reattendance without increasing the severity of the symptoms.

Despite the clinically experienced and now also well-documented high frequency of spontaneous cure (Rietveld et al. 2005; Rose et al. 2005; Everitt et al. 2006), all questions about the risk of serious adverse events in those not receiving antibiotic treatment have not been fully addressed (Sheikh & Hurwitz 2005). The effect of a general non-prescription attitude on transmission rates of pathogens also remains to be clarified (Rose et al. 2005). So far, it has therefore been the prevailing opinion in both the medical profession and the public that acute bacterial conjunctivitis should preferably be treated with topical antibiotics (Horvén 1994; Ehlers & Bek 2004). In addition to the moderately improved clinical response, topical antibiotic treatment may be socioeconomically favourable, because the risk of spreading the infection is probably reduced and the course of the disease is often shortened. Therefore, absence from work due to illness is reduced, particularly because children with acute conjunctivitis may return to kindergarten after only 1–2 days of treatment (in many countries, children are denied admittance to kindergarten or junior school before they have been treated with antibiotics or the signs of conjunctivitis have disappeared) (Lie 1994; Rose et al. 2005). On the other hand, in countries where the national health system carries the expenses of both consultations and medications, the negative socioeconomic consequences of an active consultation and treatment strategy are easily seen. Other negative sides of an active prescription policy include the patients’ medical expenses, increased medical profession workload, medicalization of a minor illness, the risk of adverse reactions to the antibiotics used and
the risk of widespread microbiological resistance. The difficulty in making a correct clinical distinction between a bacterial and a viral conjunctivitis without an available slit lamp and time-consuming laboratory tests is also a point in favour of a more expectant treatment attitude. A qualitative study of patients’ perceptions of acute infectious conjunctivitis (Everitt et al. 2003) showed that patients generally regard acute conjunctivitis as a minor disease, but they still commonly believe that it will not heal spontaneously, and accordingly they seek medical help. However, when the self-limiting nature of the condition is explained, they often express a preference to wait a few days before seeking medical attention or being treated with topical antibiotics. As mentioned earlier, concurrent otitis media occurs relatively frequently in paediatric patients with acute bacterial conjunctivitis caused by H. influenzae (Block et al. 2000; Buznach et al. 2005). In a study comparing the efficacy of short-term oral cefixime therapy with topical use of polymyxin-bacitracin, the frequency of acute otitis media developing during the first 15 days following topical or systemic antibiotic treatment was almost identical (Wald et al. 2001). The pros and cons of prescribing topical antibiotics to patients with suspected acute bacterial conjunctivitis may be summarized as in Table 1. A highly personal view on the treatment of this condition is presented in Table 2.

### Choice of topical antibiotics
In a double-blind study of patients with acute bacterial conjunctivitis, Papa et al. (2002) found netilmicin eye drops to be significantly more effective than gentamycin in both eradicating infection and ameliorating signs and symptoms. On the other hand, numerous clinical studies show no significant differences between the clinical effect of various antibiotic eye drops in patients with suspected acute bacterial conjunctivitis (Leibowitz 1991; Miller et al. 1992a; Miller et al. 1992b; Horven 1993; Carr 1998; Wall et al. 1998; Jackson et al. 2002; Normann et al. 2002). The choice of treatment will therefore be influenced by the ease of medication, side-effects, general microbiological considerations and price.

### Table 1. The pros and cons of topical antibiotics in suspected acute bacterial conjunctivitis.

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<th>Immediate antibacterial treatment</th>
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#### Immediate antibacterial treatment
Pros:
- More rapidly reduced bacterial growth
- Reduced transmission rates?
- Reduced risk of keratitis and other complications?
- Increased early clinical remission
- Reduced time out of work or education
- Earlier restart of contact lens wear
- Reduced symptoms and worries
- Early return to kindergarten/junior school

Less parental time out of work
- Socioeconomically favourable

Cons:
- Increased ‘burden’ on the healthcare system
- Socioeconomically unfavourable (if society pays medication and GP fees)
- Often unnecessary use of topical antibiotics
- Patient adverse effects
- Negative influence on the normal flora of both patient and milieu
- Increased risk of bacterial resistance

#### Delayed antibacterial treatment
Pros:
- Reduced use of topical antibiotics
  (about 50%?)
- Reduced medicalization of an ‘innocent’ condition
- Improved patient ‘education’ and responsibility

Cons:
- Little or no reduction of health service attendance
- Increased time out of work/education/kindergarten

#### No antibacterial treatment
Pros:
- Very high percentage of spontaneous clinical cure ≤ 1 week
- Less antibiotic ‘load’ on patient and society
- No adverse events related to topical antibiotics

Cons:
- Increased time out of work/education/kindergarten
- Increased risk of transmitting the infection (?)
- At least a theoretically increased risk of complications

With the exception of fusidic acid, most commercially available antibiotic eye drops should initially be applied at least six times daily. Fucithalmic® is an aqueous suspension of microcrystalline fusidic acid formulated as viscous eye drops. A protracted release is thereby obtained, giving an adequate concentration of fusidic acid for more than 12 hrs in tear fluid (Thorn & Johansen 1997). Therefore, Fucithalmic® needs only to be applied twice daily, and in addition gives far less initial blurring of vision than the use of eye ointments. A novel enhanced viscosity ophthalmic formulation of tobramycin given twice daily was also shown by Kernt et al. (2005) to be as effective as ordinary tobramycin eye drops used four times daily for acute bacterial conjunctivitis. Recently, an ordinary ophthalmic formulation of gatifloxacin administered twice daily proved to be as effective as the identical medication administered four times a day (Yee et al. 2005).

Acute bacterial conjunctivitis in young children is most frequently caused by H. influenzae, which in vitro susceptibility tests commonly classify as resistant to fusidic acid. On the other hand, both clinical experience and treatment studies show that even such cases respond well to Fucithalmic® eye drops (Horven 1993; Jackson et al. 2002). This is probably due to the fact that conventional fusidic acid susceptibility tests generally use 1 µg/ml as the breakpoint for susceptibility (Horven 1993), while concentrations in conjunctival fluid of about 15 µg/ml after 1 hr, 10 µg/ml after 6 hrs and 6 µg/ml after 12 hrs are obtained after one drop of Fucithalmic® (Thorn & Johansen 1997). In vitro studies have shown H. influenzae to be susceptible to fusidic acid in concentrations of approximately 8 µg/ml (Horven 1993). A general observation in medical treatment is that the fewer the prescribed daily doses, the better the patient compliance. In glaucoma treatment it has
been shown that compliance is significantly improved if the treatment schedule is reduced from three or four times a day to twice a day (Norell 1981; MacKean & Elkingston 1983; Kass et al. 1987) and that the midday dose is particularly likely to be omitted (Rotchford & Murphy 1998). Correspondingly, several studies have shown a slight, but statistically significant, improvement of treatment compliance by using Fucithalmic® rather than chloramphenicol eye drops in acute bacterial conjunctivitis (Kass et al. 1987) and that the midday schedule is reduced from three or four times a day to twice a day (Norell et al. 2002). Fucithalmic® therefore appears to be an attractive therapeutic alternative in most cases of acute bacterial conjunctivitis, particularly in children and in the elderly, who need assistance to administer the eye drops. In addition to the antibiotic action, the lubricating effect of the viscous formulation probably contributes to the subjectively improved condition of the patients.

Systemic use of fusidic acid is an important therapeutic option in patients with severe S. aureus infections, particularly osteomyelitis. However, it has been known for several decades that because of the high spontaneous mutation rate if fusidic acid is given as systemic monotherapy, the drug should always be given in combination with other antistaphylococcal drugs (Brown & Thomas 2002; Dobie & Gray 2004; Howden & Grayson 2006). During the last decade, a markedly increased incidence of fusidic acid-resistant S. aureus has been reported in many countries, while only low rates of fusidic acid resistance have been found in the USA, where fusidic acid is not generally available as a therapeutic option (Ravenscroft et al. 2000; Rortveit & Rortveit 2003; Shah & Mohanraj 2003; Dobie & Gray 2004; El-Zimaity et al. 2004; Zinn et al. 2004). It is commonly believed that long-term topical fusidic acid monotherapy is the main cause of the increasing resistance seen in many countries, particularly the widespread use of fusidic acid in chronic skin infections such as impetigo, folliculitis and crural ulcers (Ravenscroft et al. 2000: Brown & Thomas 2002; Mason & Howard 2004; Howden & Grayson 2006). The use of fusidic acid in patients with acute conjunctivitis has so far not been implicated as an important source of increased staphylococcal resistance, most probably because Fucithalmic® delivers a high topical drug concentration and is usually only prescribed for short-term use.

Although the simple treatment schedule (morning and evening) is an important argument in favour of Fucithalmic® in the treatment of acute bacterial conjunctivitis, it should be emphasized that chloramphenicol eye drops are also an excellent choice in the treatment of this disease. The effect of chloramphenicol is as good as that obtained with both Fucithalmic® and more recent, broad-spectrum antibiotics such as ciprofloxacin, norfloxacin and tobramycin (Miller et al. 1992b; Horven 1993; Carr 1998; Orden Martinez et al. 2004). The greatest disadvantage of chloramphenicol eye drops is the need for frequent application, which may increase the risk of suboptimal patient compliance. However, Larum et al. (1994) reported a satisfactory clinical effect even with a simplified regimen (four times daily), although the success rate was slightly lower than that obtained by the ordinary chloramphenicol treatment regime.

Chloramphenicol eye drops are the medication of choice in acute bacterial conjunctivitis in many countries, having more than a 90% market share in Australia and almost a 70% market share in the UK (Sheikh & Hurwitz 2001). Chloramphenicol also represents more than 50% of the topical ocular antibiotics prescribed in Ireland, and is the topical medication used in about 55% of patients treated for an acute red eye in England (Doona & Walsh 1995). On the other hand, as a result of the fear of serious systemic side-effects, particularly aplastic anaemia and ‘grey baby syndrome’, topical treatment with chloramphenicol is rarely used in the USA and some other countries (Rayner & Buckley 1996; Doona & Walsh 1998). The relationship between oral use of chloramphenicol and severe, often fatal, aplastic anaemia has been known for more than 50 years (Ritch et al. 1950). Later, the incidence of aplastic anaemia following oral chloramphenicol therapy has been estimated to be about one in 36 000 patients (Wallerstein et al. 1969), which is approximately 13 times greater than the risk of idiopathic aplastic anaemia in the whole population (Fraunfelder et al. 1982; Doona & Walsh 1995). A reversible bone marrow disease mainly suppressing the red blood cell line is caused by a dose-related response, and has never been suspected to be caused by topical chloramphenicol use. On the other hand, a progressive and often fatal bone marrow aplasia affecting all three haematopoetic lines is an idiosyncratic reaction, which may conceivably be precipitated even by topical use (Stern & Killingsworth 1989). It has been proposed that aplastic anaemia triggered by topical chloramphenicol medication may be the result of an individual metabolic predisposition and that the idiosyncratic reaction therefore only occurs in genetically predisposed subjects (Yunis 1973; Fraunfelder et al. 1993). Several reports have suggested a relationship between aplastic anaemia and the use of eye drops or ointment containing chloramphenicol (Rosenthal & Blackman 1965; Carpenter 1975; Abrams et al. 1980; Fraunfelder et al. 1982). However, the aetiological role of chloramphenicol in these published cases has been questioned, particularly because many of the patients had also used several systemic medications, or had extraocular diseases or a family history of blood dyscrasias (Besamusca & Bastiaensen 1986; Buckley et al. 1995; Rayner & Buckley 1996; Lancaster et al. 1998; Wiholm et al. 1998).

Two population studies published by Wiholm et al. (1998) did not support the claim that chloramphenicol eye drops increase the risk of aplastic anaemia. Furthermore, in a survey including about 400 general practices in the UK between 1988 and 1995, a total of 442 543 patients received 674 148 prescriptions for chloramphenicol eye drops (Lancaster et al. 1998). Among these, three patients with serious haematological suppression were detected. The authors conclude that even in the unlikely event that all these three cases were caused by chloramphenicol eye drops, the risk of serious haematological toxicity is small. A Dutch regional retrospective case-control study identified 12 patients with aplastic anaemia and 190 patients with other cytopenic dyscrasias during a 4 year study period (Besamusca & Bastiaensen 1986).
None of these cases were unequivocally related to the topical use of chloramphenicol, which on a yearly basis was used by one out of 29 patients included in the survey; the frequency of topical chloramphenicol use was approximately the same in patients with and without blood dyscrasias. Therefore, although the occurrence of non-dose-related cases of idiiosyncratic aplastic anaemia can not be totally excluded, it must evidently be extremely rare (Walker et al. 1998).

In conclusion, topical ophthalmic use of chloramphenicol appears to be a safe, effective and cheap treatment in patients with external ocular infections, but the medication should not be given to individuals with a personal or family history indicating haematological disease (Buckley et al. 1995).

In the USA and many other countries, eye drops containing ciprofloxacin, norfloxacin, gentamicin, tobramycin and other broad-spectrum antibacterial agents are frequently used in acute bacterial conjunctivitis. Because these medications are often used in topical or systemic treatment of more serious infections, the unnecessary development of bacterial resistance is highly undesirable. Increasing occurrence of ciprofloxacin-resistant P. aeruginosa has recently been reported by several authors. Chaudhry et al. (1999) found that while only one of 227 (0.44%) ocular isolates was resistant to ciprofloxacin from 1991 to 1994, eight of 196 (4.1%) ocular isolates showed in vitro resistance from 1995 to 1998. Resistance to ciprofloxacin implied resistance also to most other (at that time) readily available antibacterial agents. As much as 96% of these isolates was resistant to ciprofloxacin from 1991 to 1994. Among others, O'Brien & Hahn (2005) have suggested that fluoroquinolones should not be used routinely for bacterial conjunctivitis, but should be reserved for particularly severe cases. In my opinion, neither fluoroquinolones nor aminoglycosides should be used in the treatment of uncomplicated acute bacterial conjunctivitis, and topical administration of these medications should be restricted to more serious eye infections and to cases of conjunctivitis in patients not tolerating or improving on fusidic acid and chloramphenicol treatment.

A 5 year review of the in vitro efficacy of fluoroquinolones on 1053 ocular isolates obtained in 1993–1997 from 825 corneal ulcers (Goldstein et al. 1999), both drugs were highly effective against S. aureus, eradicating all strains present at baseline. Recent in vitro studies of bacterial isolates from patients with acute conjunctivitis showed that the fourth-generation fluoroquinolones (gatifloxacin and moxifloxacin) had somewhat better in vitro efficacy than earlier fluoroquinolones against G+ isolates, but not against H. influenzae (Kowalski et al. 2005).

Several other studies have also shown alarmingly high and increasing frequencies of antibiotic resistance among bacteria isolated from patients with presumed bacterial conjunctivitis. Block et al. (2000) reported that the occurrence of beta-lactamase-producing H. influenzae isolated from children with acute conjunctivitis increased from 44% in the late 1980s to 69% at the end of their study, and that the frequency of penicillin-non-susceptible S. pneumoniae (PNSP) then was three times higher than that found 5 years earlier (Doern et al. 1996). Their study also showed diminished antibacterial activity of gentamicin, tobramycin and polymyxin B. In conjunctival cultures from 428 children aged 2–36 months with suspected acute bacterial conjunctivitis, Buznach et al. (2005) found beta-lactamase production in 29% of H. influenzae isolates, while penicillin non-susceptibility was observed in 60% of S. pneumoniae isolates. As much as 96% of the H. influenzae isolates and 97% of the S. pneumoniae isolates showed in vitro susceptibility to chloramphenicol. Every antibacterial agent will to some extent influence the ecological balance both in the patient’s normal bacterial flora and in the surrounding milieu. Broad-spectrum medications with a large ‘ecological shadow’, such as fluoroquinolones and tetracyclines, have a greater tendency than agents will a smaller ecoshadow to cause bacterial resistance as well as altering the normal bacterial flora (Midttvedt 2004). Among others, O’Brien & Hahn (2005) have suggested that fluoroquinolones should not be used routinely for bacterial conjunctivitis, but should be reserved for particularly severe cases. In my opinion, neither fluoroquinolones nor aminoglycosides should be used in the treatment of uncomplicated acute bacterial conjunctivitis, and topical administration of these medications should be restricted to more serious eye infections and to cases of conjunctivitis in patients not tolerating or improving on fusidic acid and chloramphenicol treatment.

**References**


